## REMARKS

Claim 1 is amended to incorporate language from claims 3 and 8 (now canceled). Claims 3 and 8 are cancelled. Claim 40 is also cancelled. Claims 4-7, 30-31, 38, 41-47, 112-113 (formerly claims 106 and 107, respectively) have been amended to improve clarity and dependency as needed. Support therefore can be found throughout the application including the Drawings and claims as filed originally.

In particular, claims 106 and 107 (on the bottom of p. 78 of the Application), as originally filed, should have been numbered as claims 112 and 113, respectively. The claims have been amended to correct an inadvertent claim numbering oversight.

No new matter has been added by virtue of these amendments and their entry is respectfully requested.

As an initial matter, Applicants wish to point out submission of supplemental IDS citing the following references: Zumla et al., J. Immunol. Methods, Vol. 149, pp. 69-76 (1992); Peterson et al., TIG February, Vol. 13 No. 2, pp. 61-66 (1997); and Mendez et al., Nature Genetics, Vol. 15, pp. 146-156 (1997). Consideration at this time is requested.

The Action mentions on page 2 of the Office Action that the listed claims "...have only been examined to the extent that they read on the elected subject matter." While Applicants are grateful for this statement, it is expected that the claims will be examined up to and including their full breadth prior to allowance

## Claim Objections

All issues raised by the Examiner have been addressed.

**I. Rejection of Claims 1-7, 30-31, 38-39, 42-47, and 112 Under 35 U.S.C. 103(a).**

Claims 1-7, 30-31, 38-39, 42-47, and 112 stand rejected as obvious over Littman et al. (U.S. 5,859,312), in view of Mombaerts et al. (Cell, Vol. 75, 275-282, October 22, 1993), and McMurry et al. (Mol. Cell. Biol., Vol. 17 (8), 4533-4561, August 1997). While Applicants respectfully disagree with the position taken, basis for it has been addressed by this submission.

In particular, claim 1 has been amended with language from canceled claims 3 and 8. Claim 8 was not subject to the instant obviousness rejection. Accordingly, there the rejection has been addressed. Reconsideration and withdrawal of the rejection are respectfully requested.

**II. Rejection of Claims 1-2, 5, 7-8, 30-31, 38-45 Under 35 U.S.C. 103(a)**

Claims 1-2, 5, 7-8, 30-31, 38-45 stand rejected as obvious over Littman et al., in view of Mombaerts et al., and Madsen et al. (Nat. Genetics, Vol. 23, 343-347, 1999). Applicants respectfully disagree with the rejection. However, basis for it has been addressed i.e., claim 1 has been amended with language from canceled claims 3 and 8. Since claim 3 was not subject to the instant obviousness rejection, the rejection is moot. Reconsideration and withdrawal are respectfully requested

**III. Rejection of Claims 1-8, 30-31, 38-47, and 112-113 under 35 U.S.C. 112**

Claims 1-8, 30-31, 38-47, and 112-113 under 35 U.S.C. 112, first paragraph, stand rejected as not being enabled by the specification as filed. Applicants respectfully disagree.

As understood, the position taken by the Office is that specification does not provide enough information about:

> **(a)** murine or human TCR delta or gamma loci, or for rearranged human TCR alpha or beta loci or for any of the materials such as cosmids, primers, or vectors, necessary to isolate and manipulate such DNA sequences. See the Action at pg. 10, first full paragraph.

The Office has further alleged that the specification:

**(b)** fails to provide an enabling disclosure for transgenic mice which comprise

> unrearranged human TCR alpha or beta loci comprising a plurality of V, D, and/or J, and C genes, and wherein the mice are capable of productively rearranging (the human loci and producing mature T cells which express human TCR on the cell surface... Action at pgs. 10-11, bridging paragraph.

Turning to the first ground of rejection, the concern has been addressed by this submission. That is amended claim 1 recites a transgenic animal with heterologous T-cell receptors that include human alpha and beta chain derived from unrearranged human T-cell receptor loci. The specification clearly shows how to make and use animals with such specific T-cell receptors. Accordingly, there is no basis for maintaining the enablement rejection as to the first basis of the rejection.

Regarding the second basis of rejection, Applicants must respectfully disagree.

At pg. 10, last line to pg. 11, line 3, the USPTO has pointed out that the specification "provides no actual data for any mouse made according to the disclosed methods." In response, Applicants respectfully point out that compliance with the enablement requirement of 35 USC §112, first paragraph, does not turn on whether or not a patent application includes an example. An example may be working or prophetic and still satisfy the statute. See MPEP 2164.02, for instance.

That said, the instant application fully satisfies the "how to make" and "how to use" requirements of 35 USC §112, first paragraph, especially in view of the amended claims.

For instance, Figure 1 and its supporting disclosure provide a detailed overview of the main procedural steps used in the construction of certain T-cell receptor alpha constructs. Methods for incorporating transgenes into appropriate germlines are also provided. See pgs. 20-21, bridging paragraph. Other particular transgenic methods are disclosed as well. See pg. 21, lines 23-36. Strategies for inactivating germlines via "knockout" technologies are also provided. At pg. 21, last line to pg. 24, line 27. Preferred primers, vectors, and other suitable nucleic acid reagents have been provided (see pg. 24, line 29 to pg. 26, line 15) as well as illustrative mouse strains for use with the invention. At pg. 26, lines 17-24. Various TCR-based materials have also been disclosed. See pg.

24, line 26 to pg. 30, line 20. Production and use of resulting mouse strains have also been provided. See pg. 30, line 22 to pg. 32, line 22.

Additionally, the specification provides ten working examples that show how to make and use (1) mice with inactivated alpha and beta TCR chains, (2) vectors that express human TCR, and (3) mice that express human TCR genes. See Examples 1-7, 10. Use of such mice is provided in Example 8, for instance. The specification also provides how to make and use HLA expressing mice. Example 9.

In view thereof, the specification satisfies the requirements of 35 USC §112, first paragraph, especially as to the amended claims.

At pgs. 11-12, the USPTO has cited various references in support of the instant enablement rejection. Applicants respond as follows.

At pg. 11, the Office relies on Madsen et al. for the proposition that "functional rearranged human TCR are difficult to express in mouse cells". Applicants disagree with this understanding of Madsen on several grounds.

First, Madsen provides no experimental evidence whatsoever that compared the expression of human TCRs in mouse versus human cells, nor did Madsen show that human TCRs could not be functionally expressed in mouse cells. Whatever difficulties Madsen supposedly had, earlier researchers reported that they were able to express rearranged full-length human TCR genes in transfected mouse cells under certain conditions. See e.g., Zumla et al., J. Immunol. Methods, Vol. 149, pp. 69-76 (1992). Indeed, Zumla reported transfection of a TCR-negative TG40 mouse T-cell lines with expression vectors carrying the full-length rearranged human TCR alpha and beta chains driven by human and viral promoter elements. Zumla disclosed that the human TCR was successfully co-expressed at the cell surface. Thus, the position that a worker could not express functional rearranged human TCR in mouse cells is not supportable by the art of record in this case.

A copy of the Zumla reference is being provided along with the IDS submission.

Next, the USPTO cited Kouskoff, et al. for the proposition that "expression of TCR in mice was an "unwieldy endeavor" (Kouskoff et al., J. Immunol. Methods, Vol. 150, 273-280, pp. 274-275, (1995). While the Office does not define "unwieldy" the implication is that expressing a recombinant TCR in mice is too difficult to do. Applicants must disagree.

As understood, Kouskoff described experiments wherein the promoter fragments are heterologous with respect to the gene being expressed. For example, the paper cites references where the promoters from MHC class I or CD2 genes drive TCR expression. This is different from the claimed invention. For instance, expression of the transgenic TCR genes is driven by the TCR regulatory sequences, not by promoters from heterologous genes. Applicants have amended claims 1, 38 and 41 to clarify this. Thus, the concern regarding abnormal gene expression does not apply to the invention as presently claimed. Additionally, Kouskoff, as cited by the Office, is silent on the use of human TCR promoters to drive TCR gene expression in transgenic animals.

That said, the instant application fully satisfies the "how to make" and how to use" requirement of 3.5 USC §112, first paragraph, especially in view of the amended claims and in view of the supporting disclosure. For instance, the use of transgene promoters corresponding to heterologous DNA is generally discussed. See p. 10, line 26-29; p. 28, lines 26 to p. 29, line 1. The method of targeting and disrupting the endogenous promoter is generally discussed. See pp. 11, line 31 to p. 12, line 2. Figure 5 illustrates the general regions wherein regulatory sequences may be inserted into a human TCR beta YAC vector. See p. 15, line 19-20. The construction of alpha targeting vectors utilizing SV40 (P. 34, line 8) and tk promoters (p. 34, line 18) is exemplified. The construction of a Cβ chain targeting vector using a (pgk) gene promoter is exemplified. See p. 39, lines 4-5. The procedure for using PCR to detect the presence of homologous recombination, particularly of promoter sequences, is described. See pp. 24, line 21 through p. 25, lines 1-4.

Applicants respectfully disagree with the Office's use of Kouskoff on other grounds.

For instance, while Kouskoff may have found the construction and expression of certain TCR in mice an "unwieldy endeavor," other workers have not. As an illustration, Peterson et al. apparently

describes the transfer of human genomic immunoglobulin YAC DNA into transgenic mice to generate new mice with up to 1100 kb of human genomic DNA. See Peterson et al., Trends in Genetics, Vol. 13 pp. 61, 63 (1997). As disclosed, the transferred genes could display correct stage and tissue-specific expression. In the case of large genes such as those encoding human immunoglobulins, the method has been used successfully. See e.g., Mendez et al., Nature Genetics, Vol. 15 pp. 146-156 (1997). A copy of the Peterson and Mendez article is being submitted with the IDS. It is respectfully submitted that whatever problems Kouskoff experienced, a worker who read Applicants' specification could readily express TCR in mice.

Applicants respectfully disagree with the instant enablement rejection on further grounds.

For instance, the Office stated on pgs. 11-12, that T-cell selection in the thymus is mediated by cell-cell contact of the immature T-cell with resident thymocytes. Further, it is stated that cell-cell contact is mediated by the interaction of cell surface TCR on the immature T cells with peptide/MHC and CD4 or CD8 on the thymocytes. Applicants cannot agree.

Contrary to the position advanced by the USPTO, there is recognition that CD4 and CD8 molecules are not expressed on the resident thymocytes but are expressed on the T cells. Like the TCR, there is acknowledgement in the field that the CD4 and CD8 molecules mediate interactions with the MHC molecules on the resident thymocytes. Thus, when mouse CD8 (or CD4) is expressed on T-cell bearing transgenic human TCR, the mouse CD8 (or CD4) can interact with the mouse MHC on resident thymocytes to mediate T-cell selection. In addition, Applicants note that the present application does disclose embodiments in which the human TCR transgenic animals also carry transgenic human MHC and human CD8 or CD4 genes. In this specific transgenic animal, expression of the human MHC and human CD4/CD8 on the antigen presenting cells and T-cells, respectively, could further mediate positive and negative selection of T-cells coexpressing the transgenic human TCR.

It is respectfully submitted that the USPTO's concerns are misplaced as to the claimed invention.

Applicants disagree with the Office's statements on further grounds.

For instance, it has been reported that positive and negative selection of T cell carrying rearranged human TCR variable gene elements can take place in transgenic mice in the absence of human MHC or human CD4/CD8 expression. For instance, Madsen et al. (cited by the Examiner) showed that the hybrid TCR containing the human Vβ2.1 domain could be expressed by approximately 80% of T cells from human TCR transgenic mice regards of whether the human TCR variable regions was expressed the mouse MHC alone or with the HLA-DR2 or HLA-DR2/human CD4 transgenes (page 344 column 344). This result indicates that immature T cells expressing the transgenic human TCR Vβ chain are able to pass positive and negative selection in the absence of human MHC molecules and human CD4.

Research articles published after the instant application was filed support the view that a worker in possession of the instant application could make and use the invention.

For instance, Quaratino reported that human TCR transgenic mice can express antigen-specific HLA-restricted human TCR on mature T-cells in the absence of human MHC and human CD4/CD8 molecules. See Quaratino et al., Clinical and Investigative Medicine, Vol. 27, 95B Abst. T33.45 (2004).

Additionally, Roddis et al., J. Immunol., Vol. 172, pp. 155-161 (2004), generated a transgenic mouse expressing the variable domains of a human TCR (denoted GRb) specific to an influenza peptide ($NP_{383-391}$) in the context of HLA-B27.

Copies of the Quaratino and Roddis articles are being submitted as a courtesy to the Examiner.

Applicants have reviewed the cited McMurray reference (W on the Examiner's PTO-1449 form) and do not believe it is relevant to the invention as claimed.

Applicants submit that all claims are allowable as written and respectfully request early favorable action by the Examiner. If the Examiner believes that a telephone conversation with Applicants' attorney would expedite prosecution of this application, the Examiner is cordially invited

to call the undersigned attorney of record.

Applicants believe that additional fees are not required in connection with the consideration of the within matter. However, if for any reason a fee is required, a fee paid is inadequate or credit is owed for any excess fee paid, you are hereby authorized and requested to charge Deposit Account No. **04-1105.**

Respectfully submitted,

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